

Remarks/Arguments

Claims 1-8, 10-11 and 15-19 are pending in the instant application. Claims 15-18 are withdrawn as being directed to non-elected subject matter. Applicants respectfully request that if a product claim(s) is found allowable, process claims that depend from or otherwise require all the limitations of the patentable product be rejoined with the allowable product claims.

The undersigned notes all references on the Information Disclosure Statement have been considered and that the restriction requirement has been made final.

The undersigned confirms that the subject matter of all claims was commonly owned at the time any inventions covered therein were made.

Applicants respectfully traverse the rejection of claims 1-7, 11 and 19 under 35 USC 103(a) as being unpatentable over *Beauchamp et al* (WO 02/08205).

The objective of the present invention is to provide new compounds useful as inhibitors of Tie2 activity. As remarked by the Examiner on page 9 of the Office Action, there is a recognized need for new Tie2 inhibitors.

The present invention concerns a relatively small group of compounds that are all structurally closely related. All of the presently claimed compounds exhibit six essential structural elements. Those six essential structural elements are: 1) a pyrimidine ring; 2) a 2-amino substituent on the pyrimidine ring; 3) an alkynyl linker; 4) a ring A; 5) a linker group L; and 6) a ring B. All of these six features have been found to be essential for the Tie2 activity of the presently claimed compounds.

The Examiner suggests that the presently claimed invention is obvious over the disclosure of WO 02/08205 (*Beauchamp et al*). The scope and contents of Beauchamp are concerned only with new compounds for use in the treatment of neurodegenerative disorders. There is no mention of Tie2 inhibitory activity.

In *Beauchamp et al*, of the six essential structural elements of the present invention (listed above), only elements 1), 3) and 4) are always present in their compounds. Element 2) (the 2-amino substituent on the pyrimidine ring) is disclosed, but not taught as essential. Element 4) is only partially disclosed in that the group X in *Beauchamp et al*, which is equivalent to ring A, may only be an aryl and not a heteroaryl group. Essential element 5) (the linker group L) is partially

disclosed in that the group X in *Beauchamp et al* may be substituted by a group y where y is NH-CO-R₄ where R₄ is (C1-6alkyl)aryl but the other values of the linker group L of the present invention are not disclosed. Also an equivalent of the linker group L is not taught as an essential feature as *Beauchamp et al* teaches that this feature can be omitted; of the 18 possible substituents listed in *Beauchamp et al* only one of those substituents gives rise to an equivalent of the linker group L of the present invention and in addition the substituent y is disclosed as an optional feature. Essential element 6) (ring B) is also only partially disclosed. The only substituent y on the group X in *Beauchamp et al* that gives rise to an equivalent of the ring B is where y is NH-CO-R₄ where R₄ is (C1-6alkyl)aryl; i.e. there may be an aryl substituent but not a heteroaryl group, nor a cycloalkyl nor a fully or partially saturated heterocyclic ring. Again an equivalent of the ring B is not taught as an essential feature; *Beauchamp et al* clearly teaches that this feature can be omitted. Therefore, Applicants submit it is clear that the contents of *Beauchamp et al* when taken as a whole do not make the compounds of the present invention structurally obvious.

To assist in determining the teaching of *Beauchamp et al* the preferences and examples of that document should be considered. In the preferences given on pages 7 to 12 of *Beauchamp et al*, no preference is given for R⁴ being an alkyl aryl group. In addition there is no example of any compound having such a substituent in *Beauchamp et al*; such compounds are only generically disclosed therein. It is to be remembered that y only forms a linker group when it is substituted by R⁴, where R⁴ is an alkyl aryl group. All other options of R⁴ and all other options of y are outside the scope of the present invention. There are no examples in *Beauchamp et al* of a compound having all six essential structural features of the compounds of the present invention. There are no examples in *Beauchamp et al* of a compound falling within the present claims. In the majority of the examples of *Beauchamp et al* y is absent, i.e. there is no substitution on the aryl ring X. Where there is a substitution, the group y is alkyl or halo. For all of these examples there are no equivalents of the essential structural Elements 5) (linker group L) or 6) (ring B) of the instant invention.

Applicants agree with the examiner that the closest compound in *Beauchamp et al* to the instant invention is the compound of Example 31, on page 35, which is listed as preferred, but not particularly preferred, on page 11 lines 19 to 20. In this compound y is 4-acetamido. There is no equivalent of the linker group L in this compound nor an equivalent of ring B. This compound is, therefore, at least two essential structural steps away from the presently claimed invention. The

Examiner suggests that the skilled person "would be motivated to pursue each of the limited possibilities taught by Beauchamp". Thus, the examiner contends it would be obvious to structurally modify the compound of Example 31 of *Beauchamp et al* by replacing the end hydrogen of the 4-acetamido group by an aryl group as this is one of the other options for R₄ listed in *Beauchamp et al*. Since neither the group R₄ nor the compound of Example 31 is in any way highlighted in *Beauchamp et al*, why would one of skill in the art be motivated to change that one substituent on that one specific compound over any other substituent on the compound of Example 31 or for that matter, over any substituent on any other of the specifically disclosed compounds in *Beauchamp et al*. The Federal Circuit recently held that to prove prima facie obviousness for chemical cases based on structural similarity, "a showing that the prior art would have suggested making the specific [emphasis added] molecular modifications necessary to achieve the claimed invention is also required." [*Takeda Chem. Indus. et al. v. Alphapharm et al.*, No. 06-1329 (Fed. Cir. 2007, "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.")] Accordingly, contrary to the Examiner's position, since there is no suggestion to make the specific modification suggested by the Examiner, it is respectfully submitted the compounds of the instant invention are not obvious over *Beauchamp et al*.

Furthermore, when considering whether the present invention as a whole is obvious over *Beauchamp et al*, the utility of the compounds should be taken into consideration as the utility of the compounds forms a part of that invention as a whole. The activity of the compounds is not irrelevant as suggested by the Examiner. It would be irrelevant when determining the novelty of a group of compounds, but not when considering obviousness. The skilled person specifically searching for new Tie2 inhibitors upon reading the whole contents of *Beauchamp et al* would have no incentive to develop any of their compounds let alone one of their un-exemplified, non-preferred and non-specifically disclosed compounds. *Beauchamp et al* would not provide the skilled person with any expectation of success in finding compounds active as Tie2 inhibitors. There is nothing within *Beauchamp et al* or in the prior art relating to Tie2 inhibitors that would suggest the presently claimed group of compounds, most of which are many structural steps away from those of *Beauchamp et al*, would have Tie2 inhibitor activity. Furthermore, there is nothing within *Beauchamp et al* or in the prior art relating to Tie2 inhibitors that would suggest that replacement of the hydrogen group in Example 31 of *Beauchamp et al* with a 4-fluoro substituted aryl group would lead to a compound having Tie2 inhibitory activity. The skilled

person would not consider a 4-flouro substituted aryl group to be the functional equivalent of hydrogen and in any case that skilled person would not expect the substitution of a hydrogen group with a 4-flouro substituted aryl group to convert a compound having activity in the treatment of neurodegenerative disorders into a compound having Tie2 inhibitor activity. As the Examiner reasons on pages 9 and 10 of the Office Action, in the field of Tie2 inhibitors “minor structural changes can have significant impacts” on the activity of a compound even a “single modification” and that from the state of the art “it is highly unpredictable whether structurally related compounds will possess Tie2 inhibitory activity”. Using this reasoning it is clear that the presently claimed compounds are not obvious over those of *Beauchamp et al.* For the foregoing reasons, it is respectfully submitted that the difference between the present invention and *Beauchamp et al* are such that the subject matter of the present invention as a whole would not have been obvious to the person of ordinary skill in the art. Accordingly, it is respectfully requested that the rejection of claims 1-7, 11 and 19 under 35 USC 103(a) as being unpatentable over *Beauchamp et al* be reconsidered and removed.

Applicants respectfully traverse the rejection of claims 1-8, 10-11 and 19 under 35 USC 112, first paragraph, for failing to comply with the enablement requirement. The examiner argues that the instant invention is directed to “literally thousands of compounds” all of which are required to inhibit Tie2 kinase yet applicant provides in vitro data for only three. Examiner further states that “the nature of the invention is complex and, despite a recognized need for inhibitors of Tie2, there are few available. Moreover, among Tie2 inhibitors that have been developed, it is clear that minor changes can have significant impacts on their activity.” The examiner concludes that “given the complex nature of the invention,...given the limited number of working examples,... and further given the unpredictability in the art” undue experimentation would be required to practice the invention as such the elected species is not enabled for inhibiting Tie2 activity. Contrary to the Examiner’s position, applicants contend that the presently claimed relatively small group of compounds, which are all closely structurally related, each of which possess the six essential structural elements described above, have Tie2 activity. The specification contains 153 specific examples ranging over the breadth of the claimed scope. In support of their position, Applicants are providing herewith IC₅₀ data for each of the 153 exemplified compounds (including the elected species, i.e. example 22) indicating inhibition of autophosphorylation of Tie2 receptor tyrosine kinase I (See table below). The data is analogous to that given in Column 3 of Table A of the specification (page 85) for three of the exemplified compounds. This data demonstrates that Tie2 activity is possessed across the breadth of claimed scope.

| Example Number | IC₅₀ (μM) Inhibition of autophosphorylation of Tie2 receptor tyrosine kinase |
|-----------------------|--|
| 1 | 0.2004 |
| 2 | 0.7396 |
| 3 | 0.0933 |
| 4 | 0.1340 |
| 5 | 0.1189 |
| 6 | 0.5327 |
| 7 | 0.0843 |
| 8 | 0.0631 |
| 9 | 1.3666 |
| 10 | 0.1332 |
| 11 | 0.0526 |
| 12 | 3.3757 |
| 13 | 1.0397 |
| 14 | 0.0414 |
| 15 | 0.2196 |
| 16 | 0.1006 |
| 17 | 0.5557 |
| 18 | 0.0002 |
| 19 | 0.3374 |
| 20 | >16 |
| 21 | 2.6260 |
| 22 | 0.0003 |
| 23 | 1.2049 |
| 24 | 2.1520 |
| 25 | 0.0131 |
| 26 | 0.5395 |
| 27 | 0.0149 |
| 28 | 0.0157 |
| 29 | 0.1422 |
| 30 | 0.0740 |
| 31 | 0.1788 |
| 32 | 0.0444 |
| 33 | 2.5918 |
| 34 | 0.9471 |
| 35 | 0.4985 |
| 36 | 0.0568 |
| 37 | 0.0606 |
| 38 | 0.1374 |
| 39 | 0.0996 |
| 40 | 0.0150 |
| 41 | 0.1824 |
| 42 | 0.1292 |

| | |
|----|---------|
| 43 | 0.2965 |
| 44 | 0.0180 |
| 45 | 0.3253 |
| 46 | 0.0305 |
| 47 | 0.0564 |
| 48 | 3.2873 |
| 49 | 0.9956 |
| 50 | 0.8447 |
| 51 | 0.8402 |
| 52 | 1.1486 |
| 53 | 0.1798 |
| 54 | 0.8740 |
| 55 | 6.5710 |
| 56 | 0.5424 |
| 57 | 1.1072 |
| 58 | 0.3706 |
| 59 | 0.2362 |
| 60 | 0.1848 |
| 61 | 0.3535 |
| 62 | 0.0324 |
| 63 | 0.4201 |
| 64 | 0.1974 |
| 65 | 0.0275 |
| 66 | 3.4090 |
| 67 | 1.5718 |
| 68 | 0.5735 |
| 69 | 0.2515 |
| 70 | 0.0797 |
| 71 | 0.0839 |
| 72 | 1.9045 |
| 73 | 0.0001 |
| 74 | <0.0008 |
| 75 | <0.0002 |
| 76 | 0.0123 |
| 77 | 0.2648 |
| 78 | 0.0173 |
| 79 | 0.0104 |
| 80 | 0.0274 |
| 81 | 0.6219 |
| 82 | 2.1150 |
| 83 | 0.0388 |
| 84 | 0.2470 |
| 85 | <0.0005 |
| 86 | 0.0105 |
| 87 | 0.14191 |
| 88 | 0.01532 |

| | |
|-----|---------|
| 89 | 0.4485 |
| 90 | 0.00226 |
| 91 | <0.0006 |
| 92 | 0.01293 |
| 93 | 0.06501 |
| 94 | 0.59349 |
| 95 | 0.58331 |
| 96 | 0.00466 |
| 97 | 0.02783 |
| 98 | 0.03776 |
| 99 | 0.02854 |
| 100 | 0.22292 |
| 101 | 0.40933 |
| 102 | 0.00914 |
| 103 | 0.08683 |
| 104 | 0.01035 |
| 105 | 0.09859 |
| 106 | 0.06998 |
| 107 | 0.02045 |
| 108 | 0.00713 |
| 109 | 1.85257 |
| 110 | 2.189 |
| 111 | 0.29175 |
| 112 | 0.50409 |
| 113 | 0.12653 |
| 114 | 0.03559 |
| 115 | 0.0961 |
| 116 | 0.27772 |
| 117 | 0.09944 |
| 118 | 0.02296 |
| 119 | 0.00966 |
| 120 | 0.09475 |
| 121 | 0.42909 |
| 122 | 1.18645 |
| 123 | 0.47209 |
| 124 | 0.15671 |
| 125 | 0.05137 |
| 126 | 0.09482 |
| 127 | 0.30467 |
| 128 | 0.2 |
| 129 | 1.1 |
| 130 | 0.15 |
| 131 | 0.03633 |
| 132 | 0.08551 |
| 133 | 0.29084 |
| 134 | <0.0002 |

Application No. 10/596,745
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| 135 | 0.00969 |
| 136 | 0.28545 |
| 137 | 0.00422 |
| 138 | 0.0074 |
| 139 | <0.0002 |
| 140 | <0.0002 |
| 141 | <0.0002 |
| 142 | 0.29202 |
| 143 | 0.25594 |
| 144 | 0.09831 |
| 145 | 0.01711 |
| 146 | <0.0002 |
| 147 | 0.11667 |
| 148 | 0.02873 |
| 149 | 0.14408 |
| 150 | 1.2747 |
| 151 | 0.26452 |
| 152 | 0.88211 |

Accordingly, Applicants respectfully submit that claims 1-8, 10-11 and 19 are enabled for inhibiting Tie2 activity.

The provisional obvious-type double patenting rejections over copending application nos. 10/596,740, 11/185,182 and 11/815,269 are noted. Applicants would be willing to file any necessary terminal disclaimers if, and when, there is allowable subject matter, to overcome these rejections.

In view of the foregoing, Applicants believe the application is in condition for allowance, which action is respectfully requested.

Although Applicants believe no fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 101319-1P US.

Respectfully submitted,

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